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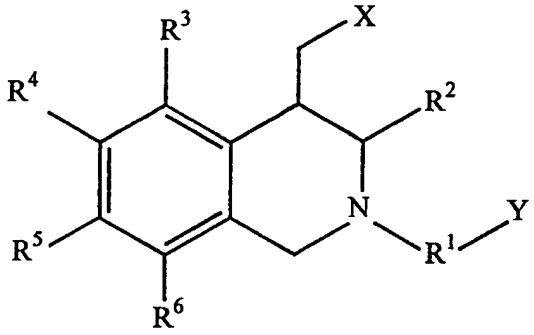
(54) Title: ISOQUINOLINE COMPOUND MELANOCORTIN RECEPTOR LIGANDS AND METHODS OF USING SAME

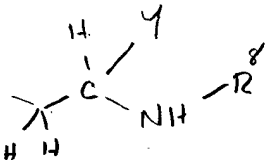
(57) Abstract

The invention relates to melanocortin receptor ligands and methods of using the ligands to alter or regulate the activity of a melanocortin receptor. The invention further relates to tetrahydroisoquinoline aromatic amines that function as melanocortin receptor ligands and as agents for controlling cytokine–regulated physiologic processes and pathologies, and combinatorial libraries thereof.

We claim:

1. An isoquinoline compound of the formula:





wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene, C_2 to C_9 alkenylene, C_2 to C_9 substituted alkenylene, C_2 to C_9 alkynylene, C_2 to C_9 substituted alkynylene, C_7 to C_{12} phenylalkylene, C_7 to C_{12} substituted phenylalkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, a heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_1 to C_6 substituted alkyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, an amino acid, aniline, substituted aniline, a heterocyclic ring, an

aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is selected from the group consisting of CH_2NHR^7 and $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

2. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl.

3. The isoquinoline compound of claim 1, wherein:

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring.

4. The isoquinoline compound of claim 1, wherein:

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom.

5. The isoquinoline compound of claim 1, wherein:

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring.

6. The isoquinoline compound of claim 1, wherein:

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

7. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

8. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1 to 4; and R^8 is selected from the group consisting of methyl, ethyl, phenethyl, 2-(N-methyl)aminoethyl, 2-aminoethyl, 2-(N-methyl)aminopropyl, hydroxyethyl, 2-(N-methyl)amino-2-phenethyl, a reduced and/or modified form of succinic anhydride, methoxyethyl, butyl, cyclohexanemethyl, benzyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl and cyclohexylethyl;

R^2 is selected from the group consisting of phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl,

2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-aminomethylphenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl, 3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl (p-anisaldehyde), 4-biphenylcarboxaldehyde, 4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthaldehyde, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl,

3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl, 5-bromo-2-furyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl, 4-amylphenyl, 4-propylaminophenyl, 4-butylaminophenyl, 4-pentylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-methoxybenzylaminophenyl, phenethylaminophenyl, 4-methoxyphenethylaminophenyl, 2-(2-norbornyl)-ethylaminophenyl, 3,4-dichlorphenethylaminophenyl, 4-benzylaminophenyl and 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino, N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino, 4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, (aminomethyl)cyclohexane, piperidinyl, morpholinyl, 1-aminopiperidinyl, diethylamino, 3-hydroxypropyl, isopropylamino,

(2-aminoethyl)-trimethylaminoethyl chloride, ammonia and hydroxy; and

Y is CH_2NH_2.

9. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of phenyl, 2-hydroxyphenyl, 1,4-benzodioxan-6-yl, 1-methyl-2-pyrrolyl, 1-naphthyl, 2,3,4-trifluorophenyl, 2,3,5-trichlorophenyl, 2,3-(methylenedioxy)phenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, 2-bromophenyl, 2-chloro-5-nitrophenyl, 2-chloro-6-fluorophenyl, 2-cyanophenyl, 2-fluorophenyl, 2-imidazolyl, 2-methoxybenzyl, 2-naphthyl, 2-thiophene-yl, 3,4-(methylenedioxy)phenyl, 3,4-dihydroxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-dihydroxyphenyl, 3,5-dichlorophenyl, 3,5-dimethoxyphenyl, 3,5-dimethyl-4-hydroxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 3-(4-methoxyphenoxy)phenyl, 3-(trifluoromethyl)phenyl, 3-bromo-4-fluorophenyl, 3-bromophenyl, 3-hydroxymethylphenyl,

3-aminomethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-methoxy-4-hydroxy-5-nitrophenyl, 3-methoxyphenyl, 3-methyl-4-methoxyphenyl, 3-methylphenyl, 3-nitro-4-chlorophenyl, 3-nitrophenyl, 3-phenoxyphenyl, 3-pyridinyl, 3-thiophene-yl, 4-(3-dimethylaminopropoxy)phenyl, 4-(dimethylamino)phenyl, 4-hydroxymethylphenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 4-ethylaminophenyl, 4-methoxyphenyl, 4-biphenyl, 4-bromophenyl, 4-aminomethylphenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-isopropylphenyl, 4-methoxy-1-naphthyl, 4-methylphenyl, 3-hydroxy-4-nitrophenyl, 4-nitrophenyl, 4-phenoxyphenyl, 4-propoxyphenyl, 4-pyridinyl, 3-methoxy-4-hydroxy-5-bromophenyl, 5-methyl-2-thiophene-yl, 5-methyl-2-furyl, 8-hydroxyquinoline-2-yl, 9-ethyl-3-carbazole-yl, 9-formyl-8-hydroxyjulolidin-yl, pyrrole-2-yl, 3-hydroxy-4-methoxyphenyl, 4-methylsulphonylphenyl, 4-methoxy-3-(sulfonic acid, Na)phenyl and 5-bromo-2-furyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is cyclohexylamino; and

Y is CH_2NH_2.

10. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of 3-(3,4-dichlorophenoxy)phenyl, 1-methyl-2-pyrrolyl, 3-phenoxyphenyl, 4-phenoxyphenyl, 3-methoxy-4-hydroxy-5-bromophenyl and 9-ethyl-3-carbazolyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is 2-hydroxybenzyl; and

Y is CH_2NH_2.

11. The isoquinoline compound of claim 1, wherein:

R^1 is selected from the group consisting of methylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is methyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl and 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of anilinyl, N-methylanilinyl, 2-chloroanilinyl, 2-methoxyanilinyl, 3-chloroanilinyl, 3-ethoxyanilinyl, 3-aminophenol, 4-chloroanilinyl, 4-methoxyanilinyl, benzylamino,

N-benzylmethylamino, 2-chlorobenzylamino, 2-(trifluoromethyl)benzylamino, 2-hydroxybenzylamino, 3-methoxybenzylamino, 3-(trifluoromethyl)benzylamino, 4-chlorobenzylamino, 4-methoxybenzylamino, 4-(trifluoromethyl)benzylamino, phenethylamino, 2-chlorophenethylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 4-methoxyphenthylamino, 3-phenyl-1-propylamino, cyclopentylamino, isopropylamino, cycloheptylamino, N-methylcyclohexylamino, cyclohexylmethylamino, piperidinyl, morpholinyl, 1-aminopiperidinyl, diethylamino, allylamino, isopropylamino, (2-aminoethyl)-trimethylammonium, ammonium and hydroxy; and

Y is CH_2NH_2.

12. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in either chiral form wherein u is selected from a number 1, 2 and 4 and R^8 is selected from the group consisting of a hydrogen atom, methyl, phenylethyl, 2-(N-methyl)aminoethyl and 2-aminoethyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl and 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and

Y is CH_2NH_2.

13. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is the number 4 and R^8 is methyl;

R^2 is selected from the group consisting of 4-propylaminophenyl, 4-butylaminophenyl, 4-cyclohexylmethylaminophenyl, 4-isobutylaminophenyl, 4-(2-methoxy)-ethylaminophenyl, 4-(4-methoxybenzyl)aminophenyl, 4-phenethylaminophenyl, 4-(4-methoxyphenethyl)aminophenyl, 2-(2-norboranyl)-ethylaminophenyl, 3,4-dichlorphenethylaminophenyl, 4-benzylaminophenyl and 4-p-chlorobenzylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and

Y is CH_2NH_2.

14. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of a hydrogen atom, methyl, ethyl, phenylethyl, 2-(N-methyl)aminoethyl, 2-aminoethyl, 2-(N-methyl)propyl, hydroxyethyl, 2-(N-methyl)amino-2-phenethyl, a reduced form of succinic anhydride, methoxyethyl, butyl, cyclohexylmethyl, benzyl, 4-bromophenethyl, 4-methoxyphenethyl, 4-chlorobenzyl, 4-methoxybenzyl, 2-naphthylethyl and cyclohexylethyl;

R^2 is selected from the group consisting of 4-biphenyl, 4-ethylaminophenyl and 4-butylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group of cyclohexylamino, ammonia and phenethylamino; and

Y is CH_2NH_2.

15. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$-(CH_2)_u-CH(NHR_8)-$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of methyl, phenethyl and benzyl;

R^2 is selected from the group consisting of 4-pentylaminophenyl, 4-ethoxyphenyl, 4-propoxyphenyl, 4-butoxyphenyl and 4-amylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is phenethylamino; and

Y is CH_2NH_2.

16. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$-(CH_2)_u-CH(NHR_8)-$

in the (r) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of methyl, 2-(N-methyl)aminoethyl, 2-aminoethyl and phenethyl;

R^2 is selected from the group consisting of 4-biphenyl, 4-ethylaminophenyl and 4-nitrophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethyl, ammonia and cyclohexylamino; and

Y is CH_2NH_2.

17. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of a hydrogen atom, phenylethyl, benzyl and 4-isobutyl-α-methylphenylethyl;

R^2 is selected from the group consisting of 2,4-dichlorophenyl, 2-bromophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-phenoxyphenyl, 4-phenoxyphenyl and 4-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of 2-(trifluoromethyl)benzylamino, 2-ethoxybenzylamino, 2-methoxyphenethylamino, 3-chlorophenethylamino, 3-methoxybenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, benzylamino, cycloheptylamino and cyclohexylamino; and

Y is CH_2NH_2.

18. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of ethyl and cyclohexylethyl;

R^2 is selected from the group consisting of 4-amylphenyl, 4-butoxyphenyl, 4-butylaminophenyl, 4-ethoxyphenyl, 4-ethylphenyl and 4-n-propoxyphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia, hydroxy and phenethylamino; and

Y is CH_2NH_2.

19. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of 4-(amino)-butyl, 4-(aminobenzyl)-butyl, 4-(diethylamino)-butyl, 4-(isopropylamino)-butyl, 4-(hydroxy)-butyl, 4-(phenethylamino)-butyl,

4-(piperidino)-butyl, 4-(t-butylamino)-butyl and 4-(aminophenyl)-butyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and phenethylamino; and

Y is CH_2NH_2.

20. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 3 and R^8 is selected from the group consisting of 4-(isopropylamino)-butyl, 4-(benzoamino)-butyl, 4-(diethylamino)-butyl, 4-(phenethylamino)-butyl, 5-(isopropylamino)-(3,4)cyclopropane-pentyl, 5-(benzoamino)-(3,4)cyclopropane-pentyl, 5-(diethylamino)-(3,4)cyclopropane-pentyl, 5-(phenethylamino)-(3,4)cyclopropane-pentyl, 2-amino-2-ethoxy-N-ethylisopropylamino- 2-amino-2-ethoxy-N-ethylbenzyl, 2-amino-2-ethoxy-N-ethyldiethyl, 2-amino-2-ethoxy-N-ethylphenethyl, (2,3)benzyl-4-isopropylamino, (2,3)benzyl-4-benzylamino, (2,3)benzyl-4-diethylamino, (2,3)benzyl-4-phenethylamino,

3-(hydroxy)-5-(isopropylamino)-3-pentyl,
3-(hydroxy)-5-(benzylamino)-3-pentyl,
3-(hydroxy)-5-(diethylamino)-3-pentyl and
3-(hydroxy)-5-(phenethylamino)-3-pentyl;

R^2 is 4-ethylaminophenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is slected from the group consisting of phenethylamino and ammonia; and

Y is CH_2NH_2.

21. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of benzyl, p-methylbenzyl, p-bromobenzyl, p-methoxybenzyl and 4-phenylbenzyl;

R^2 is selected from the group consisting of 3,5-bis(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethylamino, tyramino,

2-(4-methoxyphenyl)ethylamino,
3,4-dimethoxyphenylethylamino,
4-ethoxyphenethylamino, 4-phenoxyphenethylamino,
2-(4-chlorophenyl)ethylamino and
2-(3-methoxyphenyl)ethylamino; and

Y is CH_2NH_2.

22. The isoquinoline compound of claim 1, wherein:

R^1 is 5-(2-aminoethylamino)pentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of
2-methoxybenzylamino, 4-methoxybenzylamino,
cyclohexylamino, phenethylamino and ammonia; and

Y is CH_2NH_2.

23. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is selected from the numbers 3 and 4 and R^8 is selected from the group consisting of pentyl, 4-phenoxybutyl and 4-hydroxypentyl;

R^2 is p-(N-ethylamino)benzyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of phenethylamino and ammonia; and

Y is CH_2NH_2.

24. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of (α,α,α-trifluoro-p-tolyl)ethyl, 3-(4-methoxyphenyl)propyl, 4-biphenylmethyl, 4-biphenylethyl, 4-chlorophenylethyl, 4-phenoxybutyl, butyl, glycolyl, a hydrogen atom, hydrocinnamylmethyl, isobutylmethyl, methyl, p-methoxybenzyl, 4-hydroxybutyl and 2-(trimethyl)ethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and cycloheptylamino; and

Y is CH_2NH_2.

25. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of methyl and phenethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of 4-chlorobenzylamino, 4-methoxybenzylamino, 4-methoxyphenethylamino, phenylamino, benzylamino, cyclohexanemethylamino, cyclohexylamino, cyclooctylamino, cyclopentylamino, diethylamino, ethanolamino, isopropylamino, morpholino, n-methylanilino, n-methylcyclohexylamino, hydroxy, p-anisidino, phenethylamino, piperidino and t-butylamino; and

Y is CH_2NH_2.

26. The isoquinoline compound of claim 1, wherein:

R^1 is of the formula:

$-(CH_2)_u-CH(NHR_8)-$

in the (s) chiral form wherein u is 4 and R^8 is selected from the group consisting of (α,α,α-trifluoro-p-tolyl)ethyl, 1-adamantaneethyl, 3-(4-methoxyphenyl)propyl, 4-phenylbenzyl, 4-phenylphenethyl, 4-chlorophenethyl, 4-imidazolemethyl, 4-methoxyphenyethyl, 4-phenoxypentyl, α,α,α-trifluoro-p-toluylethyl, ethyl, benzyl, butyl, glycolyl, hydrocinnamylmethyl, isobutylmethyl, p-methoxybenzyl, phenethyl, 4-hydroxybutyl and 2-(trimethyl)ethyl;

R^2 is selected from the group consisting of 4-propoxyphenyl, 4-amylphenyl and 3,5-bistrifluoromethylphenyl;

R^3, R^4, R^5, R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of ammonia and cycloheptylamino; and

Y is CH_2NH_2.

27. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 2,4-dichlorophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

28. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

29. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

30. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-phenoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

31. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

32. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

33. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2.

34. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-phenylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

35. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-hydroxybenzylamino; and Y is CH_2NH_2.

36. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

37. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-(N-methyl)ethyl; R^2 is 4-biphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

38. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is butyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

39. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

40. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-cyclohexylethyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

41. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 2-cyclohexylethyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

42. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

43. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 2-phenethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cycloheptylamino; and Y is CH_2NH_2.

44. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-ethoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

45. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

46. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-butoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

47. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is ethyl; R^2 is 4-n-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

48. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is 4-hydroxybutyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are,

independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

49. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is pentyl; R^2 is 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is 2-phenethylamino; and Y is CH_2NH_2.

50. The isoquinoline compound of claim 1, wherein R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is 4-hydroxybutyl; R^2 is 4-pentylphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is amino; and Y is CH_2NH_2.

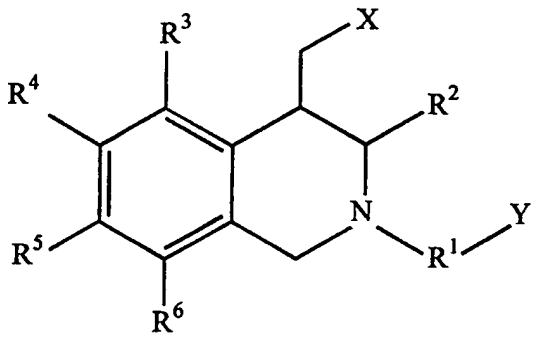
51. A method of altering the activity of a melanocortin receptor in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

52. The method of claim 51, wherein said melanocortin receptor activity regulates the activity of a cytokine.

53. The method of claim 52, wherein said melanocortin receptor ligand decreases said cytokine activity.

54. The method of claim 53, wherein said cytokine activity is tumor necrosis factor-α activity.

55. The method of claim 54, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



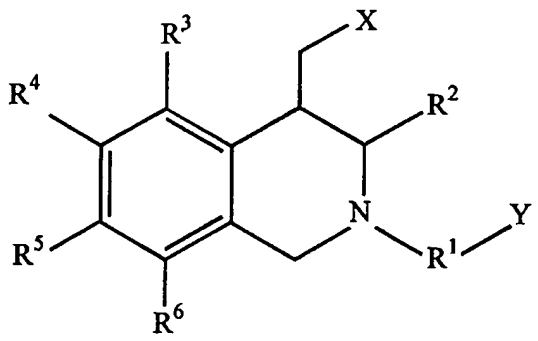
wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

56. The method of claim 52, wherein said melanocortin receptor ligand enhances said cytokine activity.

57. The method of claim 56, wherein said cytokine activity is interleukin-10 activity.

58. The method of claim 57, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:

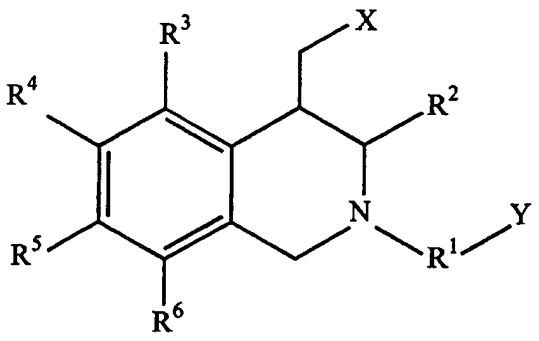


wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-ethylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

59. A method of decreasing inflammation in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

60. The method of claim 59, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:

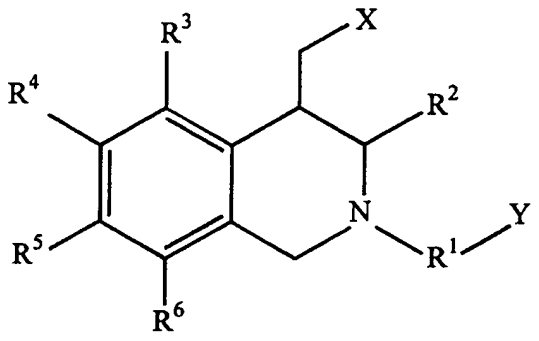


wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl, 4-propoxyphenyl and 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X selected from the group consisting of cyclohexylamino and 2-hydroxybenzylamino; and Y is CH_2NH_2.

61. A method of decreasing the body weight of a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

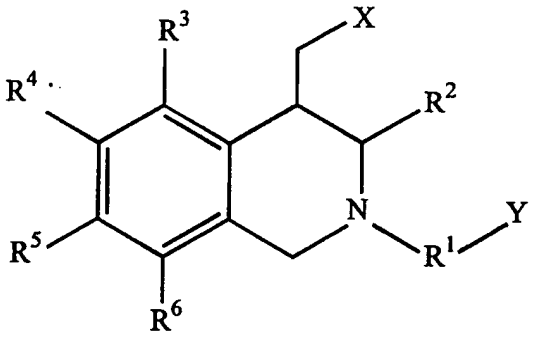
62. The method of claim 61, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 4; and R^8 is methyl; R^2 is selected from the group consisting of 2,4-dichlorophenyl, 4-biphenyl, 4-phenoxyphenyl and 4-propoxyphenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.

63. A combinatroial library comprising two or more isoquinoline compounds of the formula:



wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene, C_2 to C_9 alkenylene, C_2 to C_9 substituted alkenylene, C_2 to C_9 alkynylene, C_2 to C_9 substituted alkynylene, C_7 to C_{12} phenylalkylene, C_7 to C_{12} substituted phenylalkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, a heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_2 to C_7 alkenyl, C_2 to C_7 alkynyl, C_1 to C_6 substituted alkyl, C_2 to C_7 substituted alkenyl, C_2 to C_7 substituted alkynyl, C_1 to C_7 alkoxy, C_1 to C_7 acyloxy, C_1 to C_7 acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, C_7 to C_{12} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene,

substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_4 alkylthio, C_1 to C_4 alkylsulfonyl, C_1 to C_4 alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, an amino acid, aniline, substituted aniline, a heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

Y is selected from the group consisting of CH_2NHR^7 and $C(O)NHR^7$, wherein R^7 is a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

64. The combinatorial library of claim 63, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7

to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl.

65. The combinatorial library of claim 63, wherein:

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring.

66. The combinatorial library of claim 63, wherein:

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom.

67. The combinatorial library of claim 63, wherein:

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring.

68. The combinatorial library of claim 63, wherein:

Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

69. The combinatorial library of claim 63, wherein:

R^1 is selected from the group consisting of C_1 to C_9 alkylene, C_1 to C_9 substituted alkylene and a group of the formula:

$$-(CH_2)_u-CH(NHR_8)-$$

wherein u is selected from a number 1 to 8; and R^8 is selected from the group consisting of a hydrogen atom, C_1 to C_9 alkyl, C_1 to C_9 substituted alkyl, C_7 to C_{12} phenylalkyl and C_7 to C_{12} substituted phenylalkyl;

R^2 is selected from the group consisting of phenyl, substituted phenyl, a heterocyclic ring, amino substituted heterocyclic ring and a substituted heterocyclic ring;

R^3, R^4, R^5 and R^6 are, independently, a hydrogen atom;

X is selected from the group consisting of hydroxy, amino, protected amino, (monosubstituted)amino, (disubstituted)amino, aniline, substituted aniline, a heterocyclic ring, a substituted heterocyclic ring, an aminosubstituted heterocyclic ring, and a substituted aminosubstituted heterocyclic ring; and

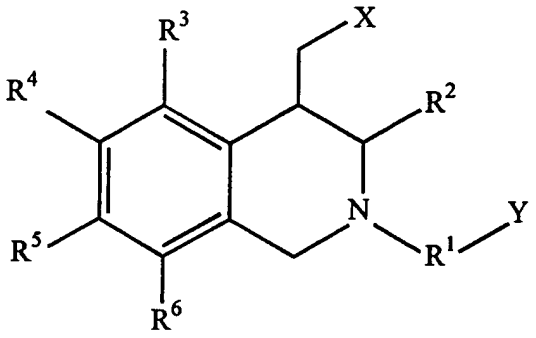
Y is CH_2NHR^7, wherein R^7 is selected from the group consisting of a hydrogen atom, C_1 to C_6 alkyl and C_1 to C_6 substituted alkyl.

70. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 1.

71. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 7.

72. A method of treating erectile dysfunction in a subject, comprising administering to the subject an effective amount of a melanocortin receptor ligand, wherein said melanocortin receptor ligand comprises the isoquinoline compound of claim 14.

73. The method of claim 72, wherein said melanocortin receptor ligand comprises an isoquinoline compound of the formula:



wherein:

R^1 is $-(CH_2)_u-CH(NHR^8)-$; u is 3; and R^8 is methyl; R^2 is 4-butylaminophenyl; R^3, R^4, R^5, R^6 are, independently, a hydrogen atom; X is cyclohexylamino; and Y is CH_2NH_2.